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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/544,899	08/08/2005	Amjad Ali	21284P	6472

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MERCK AND CO., INC  
P O BOX 2000  
RAHWAY, NJ 07065-0907

EXAMINER
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HAVLIN, ROBERT H

ART UNIT	PAPER NUMBER
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1609

MAIL DATE	DELIVERY MODE
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05/07/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/544,899

Applicant(s)

ALI ET AL.

Examiner

Robert Havlin

Art Unit

1609

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 19-21 is/are rejected.
- 7) ☒ Claim(s) 1-18 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 8/8/05.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

Art Unit: 1609

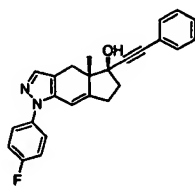
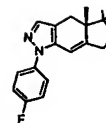
**DETAILED ACTION**

Claims 1-21 are currently pending.

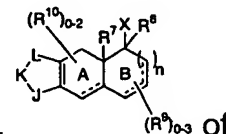
***Election/Restrictions***

1. Applicant's election with traverse of Group I:


Group I, claims 1-18 (in part), drawn to a product with the core structure of



the elected compound of example 1, , and the elected rheumatic disorders as the disease to be treated in the reply filed on 3/16/2007 is acknowledged. The traversal is on the ground(s) that the groups are properly linked to form a single general



inventive concept. This is not found persuasive because formula I, claim 1 at best only has ring A as the only common element across all of the claims (it too has variability in the dashed double/single bond, precluding it from commonality among the claims), since J, K, L, and n within the ring system vary significantly in their chemical respects, and the substituents X, R7, R8, R9, R10, Ra, Rb, Rc, Rd, etc. have chemical variability outside of a single art recognized class of compounds. Therefore,

the structural element shared by all of the alternatives is , which is not considered to be a significant structural element in light of the elected species and the totality of the claims. Thus, the determination that the commonly shared structure is not distinctive in

Art Unit: 1609

view of the prior art and the determination that unity of invention is lacking is in accordance with section (f)(i)(B)(1) of Annex B of the PCT Administrative Instructions.

The requirement is still deemed proper and is therefore made FINAL.

The elected subject matter is allowable over the prior art.

Thus the corresponding method of use claims of group V (claims 19-21) were rejoined for examination.

### ***Specification Objections***

2. The use of the trademarks BIOTAGE and SEPHADEX has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

### ***Claim Objections***

3. Claims 1-18 are objected to as being drawn to non-elected subject matter.

Applicant is advised to amend the claims to read only on the elected invention.

4. Claim 17 is objected to for improperly incorporating tables into the claims. See MPEP 2173.05(s).

### ***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

Art Unit: 1609

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide enablement for any of the method of use claims (claims 19-21). The only information provided in regard to the activity associated with the method of use claims is the following (emphasis added):

#### Biological Assays

[0372] The activity of the compounds of the present invention regarding glucocorticoid receptor affinity can be evaluated using the following human GR binding assay:

#### [0373] GR Ligand Binding Assay

[0374] For the hGRI ligand binding assay, cytosols were prepared from recombinant baculovirus expressed receptors. Frozen cell pellets were dounce homogenized in ice cold KPO.sub.4 buffer (10 mM KPO.sub.4, 20 mM sodium molybdate, 1 mM EDTA, 5 mM DTT and complete protease inhibitor tablets from Boehringer Mannheim) with a "B" plunger. The homogenates were centrifuged at 35,000.times.g for 1 h at 4.degree. C. in a JA-20 rotor. The IC.sub.50s were determined by incubating the cytosols at a final concentration of 2.5 nM [1,2,4,6,7-.sup.3H] Dexamethasone in the presence of increasing concentrations (10<sup>-11</sup> to 10<sup>-6</sup>) of cold dexamethasone or the ligands at 4.degree. C. for 24 h. Bound and free were separated by a gel filtration assay, (Geissler et al., personal communication). Half of the reaction was added to a gel filtration plate (MILLIPORE) containing sephadex G-25 beads that was previously equilibrated with KPO4 buffer containing 1 mg/ml BSA and centrifuged at 1000.times.g for 5 min.. The reaction plate was centrifuged at 1000.times.g for 5 min. and the reactions were collected in a second 96-well plate and scintillation cocktail was added and counted in (Wallac) double coincidence beta counter. The IC.sub.50 values were calculated using a 4-parameter fit program. The compounds of this invention demonstrated a range of GR affinity in the above assay with IC.sub.50 values between 10 uM and 1 nM.

Art Unit: 1609

The above quoted bold statement is far from sufficient from an enabling disclosure for treating any disease. Applicant's statement that the compounds demonstrated a range of affinity for the glucocorticoid receptor is potentially suggestive of methods of use, but in no way enables one of ordinary skill in the art to practice the methods claimed of treating disease.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

*(1) The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to methods of treating diseases associated with the glucocorticoid receptor in mammals. Thus, the claims taken together with the specification imply the ability to treat the following diseases and conditions:

tissue rejection, leukemias, lymphomas, Cushing's syndrome, acute adrenal insufficiency, congenital adrenal hyperplasia, rheumatic fever, polyarteritis nodosa, granulomatous polyarteritis, inhibition of myeloid cell lines, immune proliferation/apoptosis, HPA axis suppression and regulation, hypercortisolemia, stroke and spinal cord injury, hypercalcemia, hyperglycemia, acute adrenal insufficiency, chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia, cerebral edema, thrombocytopenia, Little's syndrome, obesity, metabolic syndrome, inflammatory bowel disease, systemic lupus erythematosus, polyarthritis nodosa, Wegener's granulomatosis, giant cell arteritis, rheumatoid arthritis, juvenile rheumatoid

Art Unit: 1609

arthritis, uveitis, hay fever, allergic rhinitis, urticaria, angioneurotic edema, chronic obstructive pulmonary disease, asthma, tendonitis, bursitis, Crohn's disease, ulcerative colitis, autoimmune chronic active hepatitis, organ transplantation, hepatitis, cirrhosis, inflammatory scalp alopecia, panniculitis, psoriasis, discoid lupus erythematosus, inflamed cysts, atopic dermatitis, pyoderma gangrenosum, pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis, herpes gestationis, eosinophilic fasciitis, relapsing polychondritis, inflammatory vasculitis, sarcoidosis, Sweet's disease, type I reactive leprosy, capillary hemangiomas, contact dermatitis, atopic dermatitis, lichen planus, exfoliative dermatitis, erythema nodosum, acne, hirsutism, toxic epidermal necrolysis, erythema multiform, cutaneous T-cell lymphoma, Human Immunodeficiency Virus (HIV), cell apoptosis, cancer, Kaposi's sarcoma, retinitis pigmentosa, cognitive performance, memory and learning enhancement, depression, addiction, mood disorders, chronic fatigue syndrome, schizophrenia, sleep disorders, and anxiety.

In addition to the selective modulation of the glucocorticoid receptor in a mammal.

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

The prior art for the methods of treating the above diseases and conditions and selective receptor modulation is incredibly broad, however much of it is extraordinarily unpredictable due to either a complete lack of understanding of the mechanisms of disease action or even the underlying basis for the disease. For example, the disease polyarteritis nodosa has an unknown cause (see Medline Encyclopedia for "polyarteritis nodosa" entry updated 8/22/2006). Thus the art is unpredictable.

*(5) The relative skill of those in the art:*

The relative skill of those in the art is very high, however, those in the art frequently have difficulty in successfully utilizing any given drug candidate in a patient to treat a disease due to the numerous complicating factors in a mammal such as bioavailability, detrimental side effects, metabolism, etc.

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for conducting a receptor assay.

Art Unit: 1609

However, the specification does not provide any indication of success in a mammal. Nor are there any working examples.

*(8) The quantity of experimentation necessary:*

Considering the state of the art as discussed by the references above, particularly with regards to treating disease and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

### ***Conclusion***

Claims 1-18 would be allowable if they were properly amended and drawn to only the elected subject matter.

### ***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Cecilia Tsang can be reached at (571)-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1609

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert Havlin  
Examiner

RH

  
CECILIA TSANG  
SUPERVISORY PATENT EXAMINER